A molecular cascade modulates MAP1B and confers resistance to mTOR inhibition in human glioblastoma.

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Authors: Dan R Laks, Juan A Oses-Prieto, Alvaro G Alvarado, Jonathan Nakashima, Shreya Chand, Daniel B Azzam, Ankur A Gholkar, Jantzen Sperry, Kirsten Ludwig, Michael C Condro, Serli Nazarian, Anjelica Cardenas, Michelle Y S Shih, Robert Damoiseaux, Bryan France, Nicholas Orozco, Koppany Visnyei, Thomas J Crisman, Fuying Gao, Jorge Z Torres, Giovanni Coppola, Alma L Burlingame, Harley I Kornblum

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Public Summary:
Clinical trials of therapies directed against a gene called mTOR in glioblastoma cancer have had disappointing results. Drug resistance of glioblastoma cancer cells to mTOR-targeted drugs has limited their usefulness. Our data show how the glioblastoma cancer cells become resistant to mTOR-targetd drugs in human glioblastoma cancer cell cultures and points us toward new therapeutic strategies.

Scientific Abstract:
Background: Clinical trials of therapies directed against nodes of the signaling axis of phosphatidylinositol-3 kinase/Akt/mammalian target of rapamycin (mTOR) in glioblastoma (GBM) have had disappointing results. Resistance to mTOR inhibitors limits their efficacy. Methods: To determine mechanisms of resistance to chronic mTOR inhibition, we performed tandem screens on patient-derived GBM cultures. Results: An unbiased phosphoproteomic screen quantified phosphorylation changes associated with chronic exposure to the mTOR inhibitor rapamycin, and our analysis implicated a role for glycogen synthase kinase (GSK)3B attenuation in mediating resistance that was confirmed by functional studies. A targeted short hairpin RNA screen and further functional studies both in vitro and in vivo demonstrated that microtubule-associated protein (MAP)1B, previously associated predominantly with neurons, is a downstream effector of GSK3B-mediated resistance. Furthermore, we provide evidence that chronic rapamycin induces microtubule stability in a MAP1B-dependent manner in GBM cells. Additional experiments explicate a signaling pathway wherein combinatorial extracellular signal-regulated kinase (ERK)/mTOR targeting abrogates inhibitory phosphorylation of GSK3B, leads to phosphorylation of MAP1B, and confers sensitization. Conclusions: These data portray a compensatory molecular signaling network that imparts resistance to chronic mTOR inhibition in primary, human GBM cell cultures and points toward new therapeutic strategies.